Paving the path for implementation of clinical genomic sequencing globally - Are we ready?

Authors: Deborah A. Marshall[1,2*], Nicolle Hua[1], James Buchanan[3], Kurt D. Christensen[4], Geert W.J. Frederix[5], Ilias Goranitis[6], Maarten J. IJzerman[7], Jeroen P. Jansen[8], Tara A. Lavelle[9], Dean A. Regier[10,11], Hadley S. Smith[4], Wendy J. Ungar[12], Deirdre Weymann[11,13], Sarah Wordsworth[14], Kathryn A. Phillips[8,15]

[1] Cumming School of Medicine, Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada.

[2] Alberta Children's Hospital Research Institute, Calgary, Alberta, Canada

[3] Health Economics and Policy Research Unit, Centre for Evaluation and Methods, Wolfson Institute of Population Health, Queen Mary University of London, London, UK

[4] PRecisiOn Medicine Translational Research (PROMoTeR) Center,

© The Author(s) 2024. Published by Oxford University Press on behalf of Project HOPE - The People-To-People Health Foundation, Inc. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/hasch/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA

[5] Epidemiology and Health Economics, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

[6] Health Economics Unit, Centre for Health Policy, University of Melbourne, Parkville, Victoria, Australia; Australian Genomics, Parkville, Victoria, Australia

[7] University of Melbourne Centre for Cancer Research, Melbourne, Australia; Erasmus School of Health Policy & Management, Rotterdam, the Netherlands

[8] Center for Translational and Policy Research on Precision Medicine (TRANSPERS), Department of Clinical Pharmacy, School of Pharmacy, University of California, San Francisco, California, USA

[9] Tufts Medical Center, Boston, Massachusetts, USA

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

[10] Cancer Control Research, BC Cancer Research Institute, Vancouver, British Columbia, Canada

[11] School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada

[12] Program of Child Health Evaluative Sciences, The Hospital for Sick Children Research Institute, Toronto, Canada; Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada

[13] Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia, Canada

[14] Health Economics Research Centre, Nuffield Department of Population Health and NIHR Biomedical Research Centre, University of Oxford, Oxford, UK

[15] Founding Editor-in-Chief, Health Affairs Scholar Emerging & Global Health Policy

*Corresponding author: Deborah A. Marshall

University of Calgary

Department of Community Health Sciences

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

3280 Hospital Dr NW

3C56 HRIC

Calgary, AB T2N 4Z6

damarsha@ucalgary.ca

Abstract

Despite the emerging evidence in recent years, successful implementation of clinical genomic sequencing (CGS) remains limited and is challenged by a range of barriers. These include a lack of standardized practices, limited economic assessments for specific indications, limited meaningful patient engagement in health policy decision-making, and the associated costs and resource demand for implementation. Although CGS is gradually becoming more available and accessible worldwide, large variations and disparities remain, and reflections on the lessons learned for successful implementation are sparse. In this commentary, members of the Global Economics and Evaluation of Clinical Genomics Sequencing Working Group (GEECS) describe the global landscape of CGS in the context of health economics and policy and propose evidence-based solutions to address existing and future barriers to CGS implementation. The topics discussed are reflected as two overarching themes: (1) system

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

readiness for CGS and (2) evidence, assessments, and approval processes. These themes highlight the need for health economics, public health, and infrastructure and operational considerations; a robust patient- and family-centered evidence base on CGS outcomes; and a comprehensive, collaborative, interdisciplinary approach.

Keywords: clinical genomic sequencing; health economics; precision medicine; global health; genomic medicine; genetic testing

Background

Clinical genome sequencing (CGS) has significantly changed genomic medicine and garnered global interest, owing to its ability to process large amounts of genomic data rapidly and simultaneously.[1,2] As a diagnostic tool in oncology, immunology, and rare diseases, CGS could enhance clinical care by offering earlier detection and reduced diagnostic odysseys, tailored treatment options, and definitive and accurate genomic etiologies and prognoses.[3–8] However, efforts to evaluate and improve implementation and access to CGS are complicated by the variability of health systems and funding capacities across countries.[9,10]

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/hasch1/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

This commentary is an international, collaborative contribution to illustrate the global landscape of CGS in clinical applications and propose economic- and policy-focused solutions where appropriate. The authors are members of the Global Economics and Evaluation of Clinical Genomics Sequencing Working Group (GEECS), which aims to improve methodologies in assessing the value of CGS to facilitate its cost-effective and equitable implementation.[11] The topics covered in this commentary reflect two themes: (1) system readiness for CGS and (2) evidence, assessments, and approval processes. We discuss several key challenges and potential solutions for addressing the slow and limited uptake of CGS globally that reflect these two themes. These challenges and solutions include the lack of harmonization and standardization around genomic data, evidentiary uncertainty about CGS which requires centralized practices and policies with collaboration amongst government bodies, laboratories, health and academic institutions, and patients to create robust evidence bases and to increase patient engagement. We also consider equity and both financial constraints and incentives to support implementation of CGS and ongoing sustainability. Although some of these topics are applicable to certain countries and types of health systems, particularly in the context of economic evaluation, the general considerations

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

regarding challenges and solutions for implementing CGS are relevant in the broad context of health policy.

System Readiness for CGS

Increasing trust in CGS through review, standardization, and transparency

It is a challenge for health systems to ensure that novel medical technologies, including CGS, are safe, effective, economically viable, and trusted by patients. In the US, concerns have emerged due to conflicting information about the limitations of genomic tests in screening for rare diseases, such as a New York Times report on the frequency and consequences of false-positive findings from non-invasive prenatal genetic tests.[12] These reports contributed to calls for greater review, standardization, and transparency of genomic testing through regulation.

Transparency of CGS could be furthered through publicly accessible genetic and laboratory test registries and regulatory and delivery system infrastructures.[13,14] For example, the National Institutes of Health Genetic Testing Registry (GTR) was developed to document and standardize data on registered laboratories and genetic tests.[14] Although regulatory oversight

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

of tests and laboratories typically falls under the jurisdiction of government agencies and professional bodies, registries such as the GTR could reveal gaps and issues in the registered tests that may prompt further inquiry and action.

However, increasing review and standardization of CGS can be complicated. Although the US Food and Drug Administration (FDA) regulates clinical tests, most genomic tests are laboratory-developed tests (LDTs) that often enter the market without regulatory review.[15] On September 29, 2023, the FDA announced its intent to provide greater oversight of LDTs through the rule-making process, with an expected final issuance in 2024.[15] Their rationale specifically notes that greater oversight is needed because of patient and provider mistrust about test safety and effectiveness.

The implications of the FDA proposal are complex and spark debate on balancing innovation and accessibility with trust in tests' safety and efficacy. Numerous responses to the proposed rules have emerged, with proponents and opponents arguing their perspectives.[16] These debates – and the implications if the rule is approved – are particularly relevant to CGS that are classified as LDTs. Regardless of the mechanisms used and actions taken, acceptance and trust by patients are critical aspects of CGS adoption.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/hschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

Considerations of Equity in CGS Access and Outcomes

Health inequity is embedded in genomic medicine. The exclusion of minoritized populations from genomics research has resulted in disparities in genomic data across ancestral groups and subsequent repercussions in clinical care, such as higher rates of inconclusive genetic results in patients from ancestral groups outside of Europe.[17,18] Compounding data disparities, individuals belonging to underserved populations, including racial and ethnic minority groups, socioeconomically vulnerable groups, and rural populations, face limited access to CGS.[19–22] When patients in underserved population groups do receive testing, disparities in outcome-based diagnostic value and accessibility to follow-up care further perpetuate cycles of health inequity.[21] If not addressed, these challenges and the greater medical distrust in these populations[23,24] could impede the successful implementation of CGS.

Policymakers and other relevant parties must consider the impact on health equity when developing policies to implement and support CGS. Health economists can advance understanding of empirical impacts on equity by using equity-informative approaches to economic evaluation of CGS interventions. One type of equity-informative analysis is the distributional cost-

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

effectiveness analysis (DCEA). DCEA models the distribution of health benefits and opportunity costs across population subgroups and thus allows formal assessment of tradeoffs between efficiency and equity.[25,26] DCEA can inform health policy and implementation decisions, and by projecting the expected impact of CGS on total health and health equity, it can be used to monitor these outcomes as genomics research progresses. Future research is warranted to address the data and methodological challenges of using DCEA to evaluate CGS, and the acceptability and usefulness of DCEA output to policymakers. Results of DCEA should be considered alongside other social science research on attitudes and preferences for CGS among diverse and representative populations.

Centralized, regional sequencing and institutional-level informatics and results disclosure

Creating a diagnostic sequencing service requires significant investment in equipment and supplies, retooling of laboratories, staff training, and maintaining updated bioinformatics pipelines. Variations in services across institutions and laboratory partners, based on the patient's region of residence and insurance coverage, contribute to inconsistency and inefficiency.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

Establishing a single high-volume sequencing laboratory within a region or payer jurisdiction with cloud-based data storage can reduce procurement, supply, and contract costs, and enhance standardized procedures for staff training and pipeline maintenance and updating.[27–29] An online regional accessioning system can be created where physicians can request sequencing for their eligible patients, allowing them to have blood drawn and shipped locally.[30] Raw results can be returned to bioinformaticians working locally with a requesting medical geneticist or specialist for clinical interpretation and reporting.[31] Alternatively, interpretation and reporting may be performed at a few academic health centers, and results returned to the ordering physician. Local solutions may be limited in terms of yielding economies of scale (e.g., smaller sample throughput) and may potentially be more expensive compared to a centralized system. Decisions in managing sequencing informatics would need to be considered in the context of the specific health system.

Understanding features for system implementation and financial incentives to drive uptake in practice

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

System readiness for CGS in practice requires an understanding of operational and logistical considerations, including the technical platform, sample collection and preparation, and the testing site and methodologies. The future use of CGS in health systems requires (1) infrastructure for a community of practice involving health professionals in various specialties; (2) operational resources for innovation, coordination, and evaluation of testing and reporting services; and, (3) a healthcare environment integrating innovation and healthcare delivery with educational and training support.[32–36] The implications of these health system factors for CGS extend beyond individuals to collective societal values and needs.[35,37] Evidence of differential use of genetic tests amongst primary care physicians reveals lower rates of referral and testing for specific patient populations in the United States.[35] These findings reflect the potential for inequitable access and uptake of CGS amongst different populations and care systems that result in differential utilization of CGS. Consequently, inadequate consideration of the impacts of health system factors could affect the accessibility of CGS for specific population groups differentially. Engaging public health experts and health economists can support healthcare decision-making and develop systems for innovation and broader, more equitable use of CGS in care and preventive applications.[32]

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

Recognizing the financial structures of health systems and coverage policies is also necessary, as they incentivize hospital institutions to consider and negotiate price-volume arrangements to maintain revenues. The Medicare Benefits Schedule in Australia dictates a 75% rebate for fluorescence in-situ hybridization testing for EGFR-negative, non-small lung cancer patients.[38] This test can be performed and claimed multiple times, which might encourage higher claims than actual testing costs. This fee structure, therefore, does not optimize clinical practice and necessitates routine review and adjustments. Conversely, the Netherlands introduced a payment bundle that covers genomic tests with a fixed rebate, encouraging health institutions to consider clinical utility-driven testing strategies in balancing off CGS tests against inexpensive alternatives.[39] As current health technology assessment (HTA) practices can overlook how health system incentives are associated with utilization and uptake, simulation models, particularly systems dynamics, can fill this gap by analyzing time-to-treatment and total cost of care episodes under varying conditions in clinical services.[40–44]

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

Evidence, Assessments, and Approval Processes

Recommendations for CGS implementation need to be evaluated for impact

Professional societies and expert consortia have issued recommendations to guide CGS implementation, addressing processes such as test requisition, data management, and clinical follow-up.[45–49] However, evaluations of these recommendations are lacking due to implementation barriers, including a lack of confidence and knowledge among healthcare providers, concerns about infrastructure costs within health systems, and reluctance of payers to cover and reimburse services.[22,50–53] The lack of robust evaluations from multiple stakeholder perspectives can result in conflicting implementation approaches that increase risks for unintentional harm and reduce clinical utility while increasing costs to health systems.[54–56] For example, the American College of Medical Genetics and Genomics recommends opportunistic screening of existing genomic information for additional actionable information in a "minimum gene list" whenever whole exome or genome sequencing is conducted.[57] In contrast, the European Society of Human Genetics discourages opportunity screening except for the purposes of evidence generation to inform future policymaking.[58] Rigorous studies of CGS are needed to better

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

ensure that implementation recommendations optimize benefits and minimize risks.

Demonstrating the value of CGS from multiple perspectives through a combination of economic modeling, prospective trials, and real-world data analyses may be particularly important to help different stakeholders prioritize needed infrastructure. Until then, health systems would likely be wary about adopting emerging applications; payers would be reserved about covering these services;[50,58,59] and regulators would be cautious about approving their use.[60–62]

Addressing uncertainty in decision-making – 'daring to change' in systems and laboratories

Insurers and payers seek answers on the added value and cost-effectiveness of CGS, but estimating monetary and patient outcomes is challenging and relies on model-based economic evaluations.[63,64] Given the complexity and scope of implementation, fully and consistently capturing the added value is not always feasible, which may lead to uncertainty in decision-making for payers, hospitals, and laboratories. This uncertainty relates to the fact that choices needed to be made without having complete insight into all added values compared to current technologies. A decision is needed, followed by more

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

improvements and valuation of CGS in the patient journey with the data available.

Apart from impacts on costs and effects for society, the educational, technical, and material requirements to support CGS implementation are also substantial, and institutions may lack confidence in their financial and human resources to adopt and sustain recommendations provided by decision-makers fully.[65–67] To prevent further delays in patients' access to innovative technologies, discussions with payers and other relevant parties are therefore needed to transition towards more suitable assessment and adoption strategies in the face of this decision uncertainty.

CGS implementation and usage also require laboratories to transform their workforce and design. These changes can alleviate the financial burden to meet demand, enhance testing scope and capacity, and support ordering institutions as a valuable resource. Laboratories should consult with other stakeholders to explore solutions to address the complexities of these adjustments. Implementing CGS depends on macro-level (e.g., design, equipment) and micro-level (e.g., workforce, tasks) changes in the laboratory space, and the hope that these modifications can bring changes that cannot be empirically measured, but can, nonetheless, offer significant value.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

A unified HTA pathway and the need for life-cycle evidence

Traditional HTA processes, designed for 'on/off' health system decisions and often for drug assessments, and the siloed nature of resource allocation decisions across and within systems may limit the optimization of CGS-related health and economic outcomes.[68,69] A unified HTA pathway with model- and data-sharing is crucial to avoid opportunity costs from uncoordinated, unstandardized, and delayed prioritization of HTA assessments. Neglecting these issues may result in structural inefficiencies, with a lack of consideration for technological changes, fiscal sustainability, and evidentiary uncertainty compromising the optimal and equitable adoption of genomic technologies.[70–73]

Establishing a unified, life-cycle health technology assessment (LC-HTA) approach towards incremental evidence development, based on real-world data, could be one approach to facilitating CGS implementation.[68,71] LC-HTA is defined as standardized data and methods that enable iterative and ongoing evidence appraisals throughout technology life-cycles as part of a learning healthcare system.[68] Its framework incorporates standard HTA concepts with on-market evidence that follows initial regulatory authorization and conditional health system reimbursement and risk-based pricing strategies based on value

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

of information analysis and payers' risk tolerance for increased flexibility.[71] Managed and time-limited access in reimbursing expensive therapies is central to LC-HTA and has been piloted in many countries worldwide, including publicly funded healthcare systems, such as the UK, Canada, and Australia, and primarily private systems such as the US.[74–76] Oncology remains the most common indication for managed access, and to date, agreements have yet to consider CGS access.

Achieving LC-HTA in an international context requires capacity-building and investment in learning healthcare infrastructure to enable ongoing monitoring, evaluation, and deliberation. It also necessitates wide stakeholder engagement for endorsement, collaborative evidence generation, and cross-jurisdictional data sharing. LC-HTA deliberation processes should be embedded into health systems to adapt to the evolving field of genomic medicine. With proper design, these efforts could mitigate uncertainty and ensure value-centered and cost-effective CGS implementation in clinical practice.

Building a robust patient-centered evidence base on CGS outcomes that integrates patient perspectives and preferences

Beyond system readiness is the need for high-quality genetic testing services that value patient and family perspectives and

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

preferences – with patients and families being informed, respected, and involved in their care in meaningful ways throughout their clinical journey.[77,78] This journey involves numerous relationships and interactions, spanning diagnostic assessments, genomic testing, and complex decision-making processes. Therefore, effective, efficient, and equitable CGS implementation requires meaningful engagement of patients and families that facilitates active involvement and improvement in their care.[79,80]

The current evidence base on CGS outcomes focuses on a narrow subset of measures, such as diagnostic yield, rather than outcomes recommended by HTA agencies, such as quality-adjusted life-years (QALY).[81,82] Studies generating evidence on the health outcomes of CGS using metrics such as the QALY would significantly improve the evidence base for implementation. That said, preference-based health-related quality-of-life instruments commonly used to generate QALY weights, such as EQ-5L, might not fully capture the patient-related benefits of CGS.[83] To date, few studies have utilized instruments that thoroughly assess psychosocial outcomes or investigated the broader impacts on patients' and families' wellbeing (e.g., via non-clinical routes). However, evidence suggests these outcomes are highly valued by patients and families, along with access to genomic testing and a timely diagnosis.[84,85] The complexity of

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/hasch/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

genomic information and actionability creates challenges for its valuation, necessitating additional consideration for non-health outcomes.[86] The application of approaches, such as cost-consequences analysis or multi-criteria decision analysis – which allow evidence on QALY outcomes to be considered alongside broader measures of patient benefit – should be encouraged.

Regardless of which measures are used to quantify the benefits of CGS for patients and their families, a coordinated global effort is required to ensure a multifaceted, robust evidence base on CGS outcomes. Data collection should be harmonized where possible to ensure sufficient data are collected, keeping in mind, for example, relatively small rare-disease populations.[81,87]

Funding Disclosures and Conflicts of Interest

Deborah A. Marshall received other grants from the Canadian Institutes of Health Research (CIHR)/Genome Ontario, CIHR/Personalized Medicine in Inflammation Network, CIHR/Genome Alberta, and Genome Canada. Marshall has received non-financial support from Illumina, Inc. and ISPOR for travel expenses to attend meetings and personal fees from OHE and Analytica for manuscript writing or attending meetings. Marshall has also received an honorarium from ISPOR to teach a methods short

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

course. Marshall is also the founding Deputy Editor of Health Affairs Scholar *Emerging & Global Health Policy.*

Nicolle Hua has declared no funding or conflicts of interest.

James Buchanan has received travel expense reimbursement from Illumina, Inc. to attend meetings.

Kurt D. Christensen has received support through grants from the National Institutes of Health, and previously was supported by a grant from Sanford Health. Christensen has also received royalties from the UpToDate articles *"Secondary findings from genetic testing"* and *"Chromosomes and cell division."*

Geert W.J. Frederix reports consulting income from Illumina, Inc. and a payment from Illumina, Inc. to give a lecture about reimbursement and whole genome sequencing.

Ilias Goranitis has declared no funding or conflicts of interest.

Maarten J. IJzerman has declared no funding or conflicts of interest.

Jeroen P. Jansen acts as Chief Scientist – HEOR at the Precision Medicine Group (PMG) on a part-time paid basis and has stock options in PMG.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

Tara A. Lavelle reports research support from the National Center for Advancing Translational Sciences and has received funding from Illumina, Inc. to attend meetings.

Dean A. Regier has received travel expense reimbursement from Illumina, Inc. to attend meetings.

Hadley S. Smith has received research support from the National Institutes of Health and reports consulting income from Illumina, Inc. and RTI International.

Wendy J. Ungar is supported by a tier 1 Canada Research Chair in Economic Evaluation and Technology Assessment in Child Health and has received grants from CIHR, Genome Canada, and the Ontario Genomics Institute. Ungar has also received a speaking honorarium from the Canadian Fertility and Andrology Society, financial travel support from the UK Academy of Medical Sciences, and payment from Broadstreet HEOR Consulting for expert advice on an unrelated topic. Ungar advises on genomics and non-drug technology funding recommendations for Ontario, Canada, as Chair of the Ontario Genetics Advisory Committee and member of the Ontario Health Technology Advisory Committee, respectively.

Deirdre Weymann co-directs IMPRINT Research Consulting, reports consulting income from AstraZeneca Canada and Birota Economics

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

Group, and has received travel funding from Illumina to attend meetings.

Sarah Wordsworth has declared no funding or conflicts of interest.

Kathryn A. Phillips is the Founding Editor-in-Chief, Health Affairs Scholar *Emerging & Global Health Policy*, and reports consulting income from Illumina, Inc. and honoraria from the California Technology Assessment Forum (CTAF), which is an independent appraisal committee for the Institute for Clinical and Economic Review (ICER), all outside the submitted work.

ORCID iD

Deborah A. Marshall http://orcid.org/0000-0002-8467-8008

Wendy J. Ungar http://orcid.org/0000-0002-0762-0101

References

1. Metzker ML. Sequencing technologies - the next generation. *Nat Rev Genet*. 2010;11(1):31-46. doi:10.1038/nrg2626

2. Goodwin S, McPherson JD, McCombie WR. Coming of age: ten years of next-generation sequencing technologies. *Nat Rev Genet*. 2016;17(6):333-351. doi:10.1038/nrg.2016.49

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/hasch1/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

3. Buermans HPJ, den Dunnen JT. Next generation sequencing technology: Advances and applications. *Biochim Biophys Acta BBA - Mol Basis Dis*. 2014;1842(10):1932-1941. doi:10.1016/j.bbadis.2014.06.015

4. Mestek-Boukhibar L, Clement E, Jones WD, et al. Rapid Paediatric Sequencing (RaPS): comprehensive real-life workflow for rapid diagnosis of critically ill children. *J Med Genet*. 2018;55(11):721-728. doi:10.1136/jmedgenet-2018-105396

5. Boycott KM, Vanstone MR, Bulman DE, MacKenzie AE. Rare-disease genetics in the era of next-generation sequencing: discovery to translation. *Nat Rev Genet*. 2013;14(10):681-691. doi:10.1038/nrg3555

6. Sosinsky A, Ambrose J, Cross W, et al. Insights for precision oncology from the integration of genomic and clinical data of 13,880 tumors from the 100,000 Genomes Cancer Programme. *Nat Med*. 2024;30:279-289. doi:10.1038/s41591-023-02682-0

7. Mboowa G, Sserwadda I, Amujal M, Namatovu N. Human Genomic Loci Important in Common Infectious Diseases: Role of High-Throughput Sequencing and Genome-Wide Association Studies. *Can J Infect Dis Med Microbiol*. 2018;2018:e1875217. doi:10.1155/2018/1875217

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

8. Duan H, Li X, Mei A, et al. The diagnostic value of metagenomic next-generation sequencing in infectious diseases. *BMC Infect Dis*. 2021;21(1):62. doi:10.1186/s12879-020-05746-5

9. Phillips KA, Douglas MP, Marshall DA. Expanding Use of Clinical Genome Sequencing and the Need for More Data on Implementation. *JAMA*. 2020;324(20):2029-2030. doi:10.1001/jama.2020.19933

10. Phillips KA, Douglas MP, Wordsworth S, Buchanan J, Marshall DA. Availability and funding of clinical genomic sequencing globally. *BMJ Glob Health*. 2021;6(2):e004415. doi:10.1136/bmjgh-2020-004415

11. Global Economics and Evaluation of Clinical Genomics Sequencing Working Group (GEECS). University of California San Francisco. Published 2021. Accessed January 19, 2024. https://www.geecsecon.org

12. The New York Times. When They Warn of Rare Diseases, These Prenatal Tests Are Usually Wrong When Warning of Rare Disorders. TheUpshot. Published January 2022. Accessed January 16, 2024. https://www.nytimes.com/2022/01/01/upshot/pregnancy-birth-genetic-testing.html

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/hasch/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

13. Zonno KD, Terry SF. Transparency, Openness, and Genetic Testing. *Genet Test Mol Biomark*. 2009;13(4):433-434. doi:10.1089/gtmb.2009.1505

14. Rubinstein WS, Maglott DR, Lee JM, et al. The NIH genetic testing registry: a new, centralized database of genetic tests to enable access to comprehensive information and improve transparency. *Nucleic Acids Res*. 2013;41(D1):D925-D935. doi:10.1093/nar/gks1173

15. Laboratory Developed Tests. FDA. 2024. Published January 2024. Accessed January 18, 2024. https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests

16. Gilmore J. The Wild, Wild West of Laboratory Developed Tests. *Wash Lee Law Rev Online*. 2024;81(4):259.

17. Petrovski S, Goldstein DB. Unequal representation of genetic variation across ancestry groups creates healthcare inequality in the application of precision medicine. *Genome Biol*. 2016;17(1):157. doi:10.1186/s13059-016-1016-y

18. Khoury MJ, Bowen S, Dotson WD, et al. Health equity in the implementation of genomics and precision medicine: A public health imperative. *Genet Med*. 2022;24(8):1630-1639. doi:10.1016/j.gim.2022.04.009

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

19. Gutierrez AM, Robinson JO, Outram SM, et al. Examining access to care in clinical genomic research and medicine: Experiences from the CSER Consortium. *J Clin Transl Sci*. 2015;5(1):e193. doi:10.1017/cts.2021.855

20. Omorodion J, Dowsett L, Clark R, et al. Delayed Diagnosis and Racial Bias in Children with Genetic Conditions. *Am J Med Genet A*. 2022;188(4):1118-1123. doi:10.1002/ajmg.a.62626

21. Fraiman YS, Wojcik MH. The Influence of Social Determinants of Health on the Genetic Diagnostic Odyssey: Who Remains Undiagnosed, Why, and to What Effect? *Pediatr Res*. 2021;89(2):295-300. doi:10.1038/s41390-020-01151-5

22. Smith HS, Franciskovich R, Lewis AM, et al. Outcomes of prior authorization requests for genetic testing in outpatient pediatric genetics clinics. *Genet Med*. 2021;23(5):950-955. doi:10.1038/s41436-020-01081-x

23. Canedo JR, Miller ST, Myers HF, Sanderson M. Racial and ethnic differences in knowledge and attitudes about genetic testing in the US: Systematic review. *J Genet Couns*. 2019;28(3):587-601. doi:10.1002/jgc4.1078

24. Angelo F, Veenstra D, Knerr S, Devine B. Prevalence and prediction of medical distrust in a diverse medical genomic

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

research sample. *Genet Med*. 2022;24(7):1459-1467. doi:10.1016/j.gim.2022.03.007

25. Asaria M, Griffin S, Cookson R. Distributional Cost-Effectiveness Analysis. *Med Decis Making*. 2016;36(1):8-19. doi:10.1177/0272989X15583266

26. Cookson R, Griffin S, Norheim OF, Culyer AJ, Chalkidou K. Distributional Cost-Effectiveness Analysis Comes of Age. *Value Health*. 2021;24(1):118-120. doi:10.1016/j.jval.2020.10.001

27. Marshall CR, Bick D, Belmont JW, et al. The Medical Genome Initiative: moving whole-genome sequencing for rare disease diagnosis to the clinic. *Genome Med*. 2020;12(1):48. doi:10.1186/s13073-020-00748-z

28. Biswas S, Medne L, Devkota B, et al. A Centralized Approach for Practicing Genomic Medicine. *Pediatrics*. 2020;145(3):e20190855. doi:10.1542/peds.2019-0855

29. Beale S, Sanderson D, Sanniti A, Dundar Y, Boland A. A scoping study to explore the cost-effectiveness of next-generation sequencing compared with traditional genetic testing for the diagnosis of learning disabilities in children. *Health Technol Assess Winch Engl*. 2015;19(46):1-90. doi:10.3310/hta19460

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

30. Genome-Wide Sequencing Ontario (GSO): A clinical collaboration for rare disease diagnostics. Accessed January 18, 2024. https://gsontario.ca/

31. Bowdin S, Gilbert A, Bedoukian E, et al. Recommendations for the Integration of Genomics into Clinical Practice. *Genet Med.* 2016;18(11):1075-1084. doi:10.1038/gim.2016.17

32. Husereau D, Steuten L, Muthu V, et al. Effective and Efficient Delivery of Genome-Based Testing-What Conditions Are Necessary for Health System Readiness? *Healthcare*. 2022;10(10):2086. Doi:10.3390/healthcare10102086

33. Genomics, Health and Society: Emerging Issues for Public Policy. Policy Research Initiative, Government of Canada. Published 2003. Accessed January 13, 2024. https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=2dd53f09fa8db8e176da983797ac42151605f361

34. Bonter K, Desjardins C, Currier N, Pun J, Ashbury FD. Personalised medicine in Canada: a survey of adoption and practice in oncology, cardiology and family medicine. *BMJ Open*. 2011;1(1):e000110. doi:10.1136/bmjopen-2011-000110

35. Shields AE, Burke W, Levy DE. Differential use of available genetic tests among primary care physicians in the United

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

States: results of a national survey. *Genet Med*. 2008;10(6):404-414. doi:10.1097/GIM.0b013e3181770184

36. Wright C, Burton H, Hall A, et al. *Next Steps in the Sequence: The Implications of Whole Genome Sequencing for Health in the UK*. Published October 2011. Accessed January 12, 2024. https://www.phgfoundation.org/report/next-steps-in-the-sequence

37. Toward Equitable Innovation in Health and Medicine: A Framework. National Academies of Sciences, Engineering, and Medicine and National Academy of Medicine; 2023. doi:10.17226/27184

38. Medicare Benefits Schedule - Item 73341. Medicare Benefits Schedule, Australian Government Department of Health and Aged Care. Accessed January 16, 2024. https://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73341

39. Verrichtingencodes voor de moleculaire diagnostiek in de pathologie. Published 2023. Accessed January 14, 2024. https://pathology.nl/wp-content/uploads/2022/12/Verrichtingencodes-voor-de-moleculaire-diagnostiek-in-de-pathologie-2023_incl-colofon.pdf

40. Marshall DA, Grazziotin LR, Regier DA, et al. Addressing Challenges of Economic Evaluation in Precision Medicine Using

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

Dynamic Simulation Modeling. *Value Health*. 2020;23(5):566-573. doi:10.1016/j.jval.2020.01.016

41. Marshall DA, Burgos-Liz L, Pasupathy KS, et al. Transforming Healthcare Delivery: Integrating Dynamic Simulation Modelling and Big Data in Health Economics and Outcomes Research. *PharmacoEconomics*. 2016;34(2):115-126. doi:10.1007/s40273-015-0330-7

42. Marshall DA, Burgos-Liz L, IJzerman MJ, et al. Applying Dynamic Simulation Modeling Methods in Health Care Delivery Research—The SIMULATE Checklist: Report of the ISPOR Simulation Modeling Emerging Good Practices Task Force. *Value Health*. 2015;18(1):5-16. doi:10.1016/j.jval.2014.12.001

43. Khorshidi HA, Marshall D, Goranitis I, Schroeder B, IJzerman M. System dynamics simulation for evaluating implementation strategies of genomic sequencing: tutorial and conceptual model. *Expert Rev Pharmacoecon Outcomes Res*. 2024;24(1):37-47. doi:10.1080/14737167.2023.2267764

44. van de Ven M, IJzerman M, Retèl V, van Harten W, Koffijberg H. Developing a dynamic simulation model to support the nationwide implementation of whole genome sequencing in lung cancer. *BMC Med Res Methodol*. 2022;22:83. doi:10.1186/s12874-022-01571-3

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

45. Richards S, Aziz N, Bale S, et al. Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424. doi:10.1038/gim.2015.30

46. Souche E, Beltran S, Brosens E, et al. Recommendations for whole genome sequencing in diagnostics for rare diseases. *Eur J Hum Genet*. 2022;30(9):1017-1021. doi:10.1038/s41431-022-01113-x

47. Austin-Tse CA, Jobanputra V, Perry DL, et al. Best practices for the interpretation and reporting of clinical whole genome sequencing. *NPJ Genomic Med*. 2022;7(1):27. doi:10.1038/s41525-022-00295-z

48. Rehm HL, Berg JS, Brooks LD, et al. ClinGen — The Clinical Genome Resource. *N Engl J Med*. 2015;372(23):2235-2242. doi:10.1056/NEJMsr1406261

49. Murugan M, Babb LJ, Taylor CO, et al. Genomic considerations for FHIR®; eMERGE implementation lessons. *J Biomed Inform*. 2021;118:103795. doi:10.1016/j.jbi.2021.103795

50. Trosman JR, Weldon CB, Slavotinek A, Norton ME, Douglas MP, Phillips KA. Perspectives of US private payers on insurance coverage for pediatric and prenatal exome sequencing: Results of a study from the Program in Prenatal and Pediatric Genomic

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

Sequencing (P3EGS). *Genet Med.* 2020;22(2):283-291. doi:10.1038/s41436-019-0650-7

51. Aronson S, Babb L, Ames D, et al. Empowering genomic medicine by establishing critical sequencing result data flows: the eMERGE example. *J Am Med Inform Assoc.* 2018;25(10):1375-1381. doi:10.1093/jamia/ocy051

52. Faulkner E, Annemans L, Garrison L, et al. Challenges in the Development and Reimbursement of Personalized Medicine—Payer and Manufacturer Perspectives and Implications for Health Economics and Outcomes Research: A Report of the ISPOR Personalized Medicine Special Interest Group. *Value Health.* 2012;15(8):1162-1171. doi:10.1016/j.jval.2012.05.006

53. Kurnat-Thoma E. Educational and Ethical Considerations for Genetic Test Implementation Within Health Care Systems. *Netw Syst Med.* 2020;3(1):58-66. doi:10.1089/nsm.2019.0010

54. Wilfond BS, Fernandez CV, Green RC. Disclosing Secondary Findings from Pediatric Sequencing to Families: Considering the "Benefit to Families." *J Law Med Ethics.* 2015;43(3):552-558. doi:10.1111/jlme.12298

55. Nolan J, Buchanan J, Taylor J, et al. Secondary (additional) findings from the 100,000 Genomes Project: disease

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

manifestation, healthcare outcomes and costs of disclosure. *Genet Med.* 2023;26(3):101051. doi:10.1016/j.gim.2023.101051

56. Eddy DM. Evidence-Based Medicine: A Unified Approach. *Health Aff (Millwood).* 2005;24(1):9-17. doi:10.1377/hlthaff.24.1.9

57. Miller DT, Lee K, Gordon AS, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2021;23(8):1391-1398. doi:10.1038/s41436-021-01171-4

58. de Wert G, Dondorp W, Clarke A, et al. Opportunistic genomic screening. Recommendations of the European Society of Human Genetics. *Eur J Hum Genet.* 2021;29(3):365-377. doi:10.1038/s41431-020-00758-w58. Trosman JR, Weldon CB, Gradishar WJ, et al. From the Past to the Present: Insurer Coverage Frameworks for Next-Generation Tumor Sequencing. *Value Health.* 2018;21(9):1062-1068. doi:10.1016/j.jval.2018.06.011

59. Dhanda DS, Veenstra DL, Regier DA, Basu A, Carlson JJ. Payer Preferences and Willingness to Pay for Genomic Precision Medicine: A Discrete Choice Experiment. *J Manag Care Spec Pharm.* 2020;26(4):529-537. doi:10.18553/jmcp.2020.26.4.529

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

60. Hedblom AH, Pruneri G, Quagliata L, et al. Cancer patient management: Current use of next-generation sequencing in the EU TOP4. *J Cancer Policy*. 2023;35:100376. doi:10.1016/j.jcpo.2022.100376

61. Milko LV, Chen F, Chan K, et al. FDA oversight of NSIGHT genomic research: the need for an integrated systems approach to regulation. *NPJ Genomic Med*. 2019;4:32. doi:10.1038/s41525-019-0105-8

62. Luh F, Yen Y. FDA guidance for next generation sequencing-based testing: balancing regulation and innovation in precision medicine. *NPJ Genomic Med*. 2018;3:28. doi:10.1038/s41525-018-0067-2

63. Vozikis A, Cooper DN, Mitropoulou C, et al. Test Pricing and Reimbursement in Genomic Medicine: Towards a General Strategy. *Public Health Genomics*. 2017;19(6):352-363. doi:10.1159/000449152

64. Payne K, Gavan SP, Wright SJ, Thompson AJ. Cost-effectiveness analyses of genetic and genomic diagnostic tests. *Nat Rev Genet*. 2018;19(4):235-246. doi:10.1038/nrg.2017.108

65. Williams MS. Early Lessons from the Implementation of Genomic Medicine Programs. *Annu Rev Genomics Hum Genet*. 2019;20:389-411. doi:10.1146/annurev-genom-083118-014924

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

66. Qureshi S, Latif A, Condon L, Akyea RK, Kai J, Qureshi N. Understanding the barriers and enablers of pharmacogenomic testing in primary care: a qualitative systematic review with meta-aggregation synthesis. *Pharmacogenomics*. 2022;23(2):135-154. doi:10.2217/pgs-2021-0131

67. Manolio TA, Rowley R, Williams MS, et al. Opportunities, Resources, and Techniques for Implementing Genomics in Clinical Care. *Lancet*. 2019;394(10197):511-520. doi:10.1016/S0140-6736(19)31140-7

68. Weymann D, Pollard S, Lam H, Krebs E, Regier DA. Toward Best Practices for Economic Evaluations of Tumor-Agnostic Therapies: A Review of Current Barriers and Solutions. *Value Health*. 2023;26(11):1608-1617. doi:10.1016/j.jval.2023.07.004

69. Plun-Favreau J, Immonen-Charalambous K, Steuten L, et al. Enabling Equal Access to Molecular Diagnostics: What Are the Implications for Policy and Health Technology Assessment? *Public Health Genomics*. 2016;19(3):144-152. doi:10.1159/000446532

70. Norris S, Belcher A, Howard K, Ward RL. Evaluating genetic and genomic tests for heritable conditions in Australia: lessons learnt from health technology assessments. *J Community Genet*. 2022;13(5):503-522. doi:10.1007/s12687-021-00551-2

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

71. Kirwin E, Round J, Bond K, McCabe C. A Conceptual Framework for Life-Cycle Health Technology Assessment. *Value Health*. 2022;25(7):1116-1123. doi:10.1016/j.jval.2021.11.1373

72. Mordaunt DA, Dalziel K, Goranitis I, Stark Z. Uptake of funded genomic testing for syndromic and non-syndromic intellectual disability in Australia. *Eur J Hum Genet*. 2023;31(9):977-979. doi:10.1038/s41431-023-01417-6

73. Sampson CJ, Arnold R, Bryan S, et al. Transparency in Decision Modelling: What, Why, Who and How? *PharmacoEconomics*. 2019;37(11):1355-1369. doi:10.1007/s40273-019-00819-z

74. Regier DA, Pollard S, McPhail M, et al. A perspective on life-cycle health technology assessment and real-world evidence for precision oncology in Canada. *NPJ Precis Oncol*. 2022;6:76. doi:10.1038/s41698-022-00316-1

75. Ciulla M, Marinelli L, Di Biase G, et al. Healthcare Systems across Europe and the US: The Managed Entry Agreements Experience. *Healthcare*. 2023;11(3):447. doi:10.3390/healthcare11030447

76. Zampirolli Dias C, Godman B, Gargano LP, et al. Integrative Review of Managed Entry Agreements: Chances and Limitations. *PharmacoEconomics*. 2020;38(11):1165-1185. doi:10.1007/s40273-020-00943-1

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

77. Epstein RM, Peters E. Beyond Information: Exploring Patients' Preferences. *JAMA*. 2009;302(2):195-197. doi:10.1001/jama.2009.984

78. Lee W, Luca S, Costain G, et al. Genome sequencing among children with medical complexity: What constitutes value from parents' perspective? *J Genet Couns*. 2022;31(2):523-533. doi:10.1002/jgc4.1522

79. Carman KL, Dardess P, Maurer M, et al. Patient And Family Engagement: A Framework For Understanding The Elements And Developing Interventions And Policies. *Health Aff (Millwood)*. 2013;32(2):223-231. doi:10.1377/hlthaff.2012.1133

80. *Technical Series on Safer Primary Care: Patient Engagement*. World Health Organization. Published December 2016. Accessed January 3, 2024. https://www.who.int/publications-detail-redirect/9789241511629

81. Buchanan J, Wordsworth S. Evaluating the Outcomes Associated with Genomic Sequencing: A Roadmap for Future Research. *PharmacoEconomics Open*. 2019;3(2):129-132. doi:10.1007/s41669-018-0101-4

82. Schwarze K, Buchanan J, Taylor JC, Wordsworth S. Are whole-exome and whole-genome sequencing approaches cost-effective? A

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

systematic review of the literature. *Genet Med*. 2018;20(10):1122-1130. doi:10.1038/gim.2017.247

83. Pan T, Wu Y, Buchanan J, Goranitis I. QALYs and rare diseases: exploring the responsiveness of SF-6D, EQ-5D-5L and AQoL-8D following genomic testing for childhood and adult-onset rare genetic conditions in Australia. *Health Qual Life Outcomes*. 2023;21(1):132. doi:10.1186/s12955-023-02216-9

84. Pollard S, Weymann D, Dunne J, et al. Toward the diagnosis of rare childhood genetic diseases: what do parents value most? *Eur J Hum Genet*. 2021;29(10):1491-1501. doi:10.1038/s41431-021-00882-1

85. Marshall DA, MacDonald KV, Heidenreich S, et al. The value of diagnostic testing for parents of children with rare genetic diseases. *Genet Med*. 2019;21(12):2798-2806. doi:10.1038/s41436-019-0583-1

86. Regier DA, Weymann D, Buchanan J, Marshall DA, Wordsworth S. Valuation of Health and Nonhealth Outcomes from Next-Generation Sequencing: Approaches, Challenges, and Solutions. *Value Health*. 2018;21(9):1043-1047. doi:10.1016/j.jval.2018.06.010

87. Brazier J, Peasgood T, Mukuria C, et al. The EQ-HWB: Overview of the Development of a Measure of Health and Wellbeing

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024

and Key Results. *Value Health*. 2022;25(4):482-491.
doi:10.1016/j.jval.2022.01.009

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/healthaffairsscholar/advance-article/doi/10.1093/haschl/qxae053/7659451 by University of CA, San Francisco, Cancer Center user on 03 May 2024